Co$_2$(CO)$_8$ Mediated Pauson–Khand Reaction (PKR)

Nathan Bennett

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Pauson-Khand Reaction (PKR) General Information

Transition Metals = Co, Rh, Ti, Ru, Mo, W, Fe, Ni, Zr, Ir, Pd

Promoters = NaBH$_4$, Amines, Nitriles (CH$_3$CN), Amine N-Oxides (NMO, TMAO), Thioureas, Phosphines, Phosphites, Sulfoxides (DMSO), Sulfides, Thioacetals, Silica Gel

Solvent = Benzene, Toluene, DCM, Acetonitrile, DMSO, Methanol, Hexanes, Ethyl Acetate, etc.

Completely compatible with ethers, alcohols, 3° amines, thioethers, ketones, ketals, esters, 3° amides, aromatic rings (benzene furan, thiophene)

Partial tolerance to alkyl/aryl halides, vinyl ethers and esters, ordinary alkene and alkynes in presence of more reactive unsaturation

**PKR General Information**

*Geometry Changes*

\[
\begin{align*}
R_1 & \longrightarrow R_2 & \text{Promoter / Solvent} \\
& \text{CD atmosphere} \\
\text{Co}(\text{CO})_3 & \quad \text{Isolable} & \text{Co}(\text{CO})_3
\end{align*}
\]

*Electronic Changes – Nicholas Reaction*

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
R^2 & \quad \text{H} \\
\text{Co}(\text{CO})_3 & \quad \text{Nucleophile} \\
\text{Lewis Acid} & \quad \text{Co}(\text{CO})_3 & \quad \text{R}^1
\end{align*}
\]


---

**PKR Mechanism**

*Magnus Mechanism*

\[
\begin{align*}
\text{Isolable} & \quad \Delta & \text{Isolable} \\
& \text{R}^1 & \text{R}^2
\end{align*}
\]


PKR Mechanism

General Mechanism


PKR Mechanism

DFT Calculations

**PKR Early Work**

*Origin*

**First Example in Literature**


— Originally reported by Peter L. Pauson in 1973

— First Author: Ihsan U. Khand

— Two Other Authors: Graham R. Knox and William E. Watts

— Department of Pure and Applied Chemistry

University of Strathclyde in Glasgow, Scotland

— Pauson refers to as “Khand Reaction”

**Four Main Papers**


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**PKR Early Work**

*First Publications*

\[
\begin{align*}
&\text{(CO)}_3\text{Co}+\text{Ph} \quad \text{R}^1 = \text{H, Ph} \\
&\text{R}^2 = \text{H, Ph}
\end{align*}
\]

\[
\begin{align*}
&\text{(CO)}_3\text{Co}+\text{Ph} \quad \text{R}^1 = \text{H, Ph} \\
&\text{R}^2 = \text{H, Ph}
\end{align*}
\]

---


**PKR Early Work**
*Publication Main Results*

$$\text{R}^1\text{C}O\text{C}1\text{O}\text{C}2\text{R}^2 + \text{PhH or PhMe} \rightarrow A + B + C$$

<table>
<thead>
<tr>
<th>entry</th>
<th>$\text{R}^1$</th>
<th>$\text{R}^2$</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>Et</td>
<td>23</td>
</tr>
</tbody>
</table>


**PKR Mechanism**
*Determining Stereochemistry*

$$\text{R}^1\text{C}O\text{C}1\text{O}\text{C}2\text{R}^2 \rightarrow \text{A (Unfavored)} \rightarrow \text{B (Favored)}$$

PKR Early Work
Exo–Endo Isomerization

*Moreover when the samples of the mixture from the condensation reaction were withdrawn at intervals and examined by g.i.c. it was found that the endo-isomer was barely detectable after 1 h but increased steadily with reaction time. Thus, endo-isomer arises by catalysed isomerisation of the exo-isomer formed in the initial reaction.

This isomerisation is irreversible: a sample of pure endo-ketone was heated in the presence of octacarbonyldicobalt for 18 h showed no trace of the exo-isomer ...*

The isomerisation, unlike the condensation reaction must require the second double bond since no endo-isomer of ketone (A) was found.

Moreover it is strongly hindered by substitution: we do not detect peaks attributable to endo-isomers in the ketones from substituted acetylenes ...*  


PKR Early Work
Exo–Endo Isomerization

On working with rate enhancing procedures:

*This conflicted with the earlier conclusion that the endo-compound results from isomerisation of the exo form. Indeed, when a sample of pure exo-ketone was kept at 70 °C in the presence of octacarbonyldicobalt for 24 h no such isomerisation occurred but less than 50% of the ketone was recovered. We concluded that the previously noted change in isomer ratio of a mixed sample must have resulted from differential rate of loss of the two stereoisomers and not from isomerisation.*

**PKR Early Work**

*Other Substrates*

\[
\begin{align*}
&\text{entry} & R^1 & R^2 & \% \text{ Yield} \\
&1 & H & H & 23 \\
&2 & H & \text{Me} & 38 \\
&3 & H & \text{Ph} & 31 \\
&4 & \text{Ph} & \text{Ph} & 28
\end{align*}
\]


---

**PKR Early Work**

*First Catalytic Example*

\[
\begin{align*}
&\text{Co}_2(\text{CO})_8 \quad + \\
&\text{iso-octane, 60–70 °C} \\
&1) \quad \text{CO:} \quad (1:1) \\
&2) \quad 60–70 °C
\end{align*}
\]

<table>
<thead>
<tr>
<th>Co$_2$(CO)$_8$</th>
<th>Norbornene</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>g mmol mol %</td>
<td>g mmol</td>
<td>g % Yield</td>
</tr>
<tr>
<td>1.0 3 9.4 3 32</td>
<td>3.54 74</td>
<td></td>
</tr>
<tr>
<td>0.52 1.5 2.3 6.05 64.25</td>
<td>5.8 61.5</td>
<td></td>
</tr>
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</table>

PKR Early Work
Publication Summary

R1R2 + R1R2 PhH or PhMe

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>43</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>33</td>
<td>17</td>
<td>4.4</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
<td>45</td>
<td>13</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>28</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>Et</td>
<td>23</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

— Bulkier alkyne substituent located at C–2 position
— Exo-isomer major product
— Bis-functionalized product possible
— Dicobalt mono- and bis-norbornadiene carbonyl complexes not part of mechanism
— Endo and Exo-isomers degrade (no isomerization)
— Impact of substitution and electronics of alkene
— First catalytic example


PKR Early Work
Expanding Reaction Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>R1</th>
<th>R2</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
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<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>Et</td>
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</tr>
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<td>6</td>
<td>Me</td>
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</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>SiMe3</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>CH2=CHMe</td>
<td>a</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>CH2=CH=CHMe</td>
<td>a</td>
</tr>
</tbody>
</table>

a Unpublished results.

**PKR Early Work**

*Expanding Reaction Scope*

<table>
<thead>
<tr>
<th>entry</th>
<th>n</th>
<th>R¹</th>
<th>R²</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>H</td>
<td>H</td>
<td>23</td>
</tr>
<tr>
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<td>38</td>
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<td>H</td>
<td>Ph</td>
<td>31</td>
</tr>
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<td>4</td>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
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<td>2</td>
<td>H</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>H</td>
<td>Me</td>
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<tr>
<td>7</td>
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<td>H</td>
<td>Ph</td>
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</tbody>
</table>

*Entries 1-4, see Ref 1. Entries 5-7, see Ref 2.*


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**PKR Early Work**

*Impact of Distant Sterics*

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>% Yield</th>
<th>A</th>
<th>B</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>25</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>53</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Ph</td>
<td>44</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Ph</td>
<td>28</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

PKR Early Work
First Substituted Alkene Examples


Alkene Selectivity Using Co₂(CO)₈

<table>
<thead>
<tr>
<th>entry</th>
<th>Alkyne</th>
<th>Alkene</th>
<th>2,5-Product</th>
<th>2,4-Product</th>
<th>2,5 : 2,4</th>
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<tbody>
<tr>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Diene Reactivity**

<table>
<thead>
<tr>
<th>entry</th>
<th>Alkyne</th>
<th>Alkyne</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image3.png" alt="Product 1" /></td>
<td>Not Reported</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>Not Reported</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image5.png" alt="Product 3" /></td>
<td>R = H 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R = Me 38</td>
</tr>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image6.png" alt="Product 4" /></td>
<td>R = Ph 65</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image7.png" alt="Product 5" /></td>
<td>R¹ = H, R² = Ph 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R¹ = Me, R² = Ph 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R¹ = Ph, R² = Me 23</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image8.png" alt="Product 6" /></td>
<td>R = Me 55</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1.png" alt="Alkyne 1" /></td>
<td><img src="image2.png" alt="Alkyne 2" /></td>
<td><img src="image9.png" alt="Product 7" /></td>
<td>R = Ph 60</td>
</tr>
</tbody>
</table>


**Electronic Effects**

1,3-Diene Products

Electronic Effects

1,3–Diene Mechanism

**Electronic Effects**

1,3–Diene Products

\[
\begin{align*}
&\text{(CO)}_2\text{Co} \quad \text{Ph} \quad \text{H} \quad + \quad \text{Ph} \quad \text{(CO)}_2\text{Co} \quad \text{H} \quad + \quad \text{CN} \\
&\quad \text{(CO)}_2\text{Co} \quad \text{Ph} \quad \text{H} \quad + \quad \text{Ph} \quad \text{(CO)}_2\text{Co} \quad \text{H} \quad + \quad \text{CO}_2\text{Et} \quad \xrightarrow{\text{45% yield}} \quad \text{Ph} \quad \text{Ph} \quad \text{CO}_2\text{Et} \quad + \quad \text{Ph} \quad \text{Ph} \quad \text{CO}_2\text{Et} \\
&\text{3.5:1} \quad \text{3:1}
\end{align*}
\]


**Electronic Effects**

Substituted Styrene

\[
\begin{align*}
&\text{(CO)}_2\text{Co} \quad \text{Ph} \quad \text{H} \quad + \quad \text{Ph} \quad \text{R} \quad \xrightarrow{\text{electron-rich dienes}} \quad \text{Ph} \quad \text{H} \quad \text{C} = \text{C} \quad \text{Ph} \quad \text{R} \\
&\xrightarrow{\text{electron-rich enones}} \quad \text{Ph} \quad \text{H} \quad \text{C} = \text{C} \quad \text{Ph} \quad \text{R} \quad + \quad \text{Ph} \quad \text{H} \quad \text{C} = \text{C} \quad \text{Ar} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>Diene</th>
<th>Enone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>26</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>4-F</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>2-Cl</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>4-MeO</td>
<td>42</td>
<td>27</td>
</tr>
</tbody>
</table>

**Electronic Effects**

**Aromatic Alkenes**

\[
\text{CO}_2\text{H} + \text{Alkene} \rightarrow \text{R}^1\text{H}\text{C}^\text{1}\text{C}^\text{2}\text{C}^\text{3}\text{C}^\text{4} + \text{R}\text{Me}^1\text{C}^\text{1}\text{C}^\text{2}\text{CH}_2^3 + \text{R}^1\text{H}\text{C}^\text{1}\text{C}^\text{2}\text{C}^\text{3}\text{C}^\text{4}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>Alkene</th>
<th>% Yield</th>
<th>entry</th>
<th>R¹</th>
<th>Alkene</th>
<th>% Yield</th>
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<tbody>
<tr>
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<td></td>
<td></td>
<td>Diene</td>
<td></td>
<td></td>
<td></td>
<td>Enone</td>
</tr>
<tr>
<td>1</td>
<td>Ph</td>
<td>trans, trans: 15</td>
<td>0</td>
<td>6</td>
<td>Ph</td>
<td>Ph: 4</td>
<td>Ph: 38</td>
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<td>2</td>
<td>Ph</td>
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<td>trace</td>
<td>7</td>
<td>Me</td>
<td>Me: 0</td>
<td>Me: 35</td>
</tr>
<tr>
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<td>Ph</td>
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<td>15</td>
<td>8</td>
<td>H</td>
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<td>H: 31</td>
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<tr>
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<td>Ph</td>
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<td>9</td>
<td>Me</td>
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<td>Me</td>
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<td>Me: 26</td>
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<td>12</td>
<td>Ph</td>
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</tbody>
</table>


**Electronic Effects**

**Coordinated Substituted Styrene**

\[
\text{Co}_2\text{H} + \text{R}^1\text{Ph} \rightarrow \text{R}^1\text{H}\text{Ph}^1\text{Ph}_2^3 + \text{R}\text{Me}^1\text{H}^1\text{Ph}_2^3 + \text{R}^1\text{H}\text{Ph}^1\text{Ph}_2^3 + \text{R}\text{Me}^1\text{H}^1\text{Ph}_2^3
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>% Yield</th>
<th>Diene</th>
<th>Enone</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>32</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-Me</td>
<td>29</td>
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</tr>
<tr>
<td>3</td>
<td>4-Cl</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-F</td>
<td>44</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-MeO</td>
<td>35</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

Selectivity Summary

1,3–Diene Summary

— Alkynes
  • Bulkier substituent located at C2 position of cyclopentenone
  • Switch functionality to C3 through use of silyl protecting groups

— Alkenes
  • Aryl alkenes favor 2,5–products
  • Alkyl alkenes are generally mixtures of 2,5– and 2,4–products
  • Bidentate ligands can improve selectivity

— 1,3–Diene Products
  • EWG favor 1,3–diene
  • Styrenes have intermediate reactivity producing both 1,3–dienes and enones
  • Other aromatics have mixed reactivity greatly dependent on substrate
  • Co_2(CO)_8 does not offer the best path to diene products

PKR Mechanism

DFT Calculations

**PKR Mechanism**

*Influence of Alkene Strain on Reaction*

Strain Impact on $E_a$

- Alkene strain impacts energy of 2nd step
- Intermediate D relieves alkene strain $\rightarrow E_a$
- Co back donation $\rightarrow$ Cobaltacycle barrier
- Looking for lower LUMO of Alkene
  - $\Delta$LUMO = LUMO$_{alkene}$
- Less strained alkenes proceed at higher $T$

---

<table>
<thead>
<tr>
<th>Alkene</th>
<th>$\Delta H^\circ$ (kcal/mol)</th>
<th>Alkene</th>
<th>$\Delta H^\circ$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$</td>
<td>$-47.3$</td>
<td>$\Delta$</td>
<td>$-27.8$</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>$-32.0$</td>
<td>$\Delta$</td>
<td>$-21.7$</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>$-31.3$</td>
<td>$\Delta$</td>
<td>$-21.6$</td>
</tr>
<tr>
<td>$\Delta$</td>
<td>$-32.5$</td>
<td>$\Delta$</td>
<td>$-21.0$</td>
</tr>
</tbody>
</table>

---

**PKR Mechanism**

*Influence of Alkene Strain on Reaction*

<table>
<thead>
<tr>
<th>Alkene</th>
<th>$\Delta H^\circ_1$ (kcal/mol)</th>
<th>Alkene</th>
<th>$\Delta H^\circ_1$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$</td>
<td>$-47.3$</td>
<td>$\bigcirc$</td>
<td>$-27.8$</td>
</tr>
<tr>
<td>$\bigcirc$</td>
<td>$-32.0$</td>
<td>$\bigcirc$</td>
<td>$-21.7$</td>
</tr>
<tr>
<td>$\bigboxdot$</td>
<td>$-31.3$</td>
<td>$\bigboxdot$</td>
<td>$-21.6$</td>
</tr>
<tr>
<td>$\bigstar$</td>
<td>$-32.5$</td>
<td>$\bigstar$</td>
<td>$-21.3$</td>
</tr>
</tbody>
</table>

1. NMO, DCM, -35 °C
2. $\bigtriangleup$, DCM, -35 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>$R$</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBu</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>HO</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Ph, Si</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>HO</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>C$_6$H$_5$</td>
<td>62</td>
</tr>
</tbody>
</table>


---

**Alkene Reactivity**

*Alkene Strain Impact*

"Only strained alkenes (e.g. norbornene) are reactive under mild conditions (60–80 °C), while simple alkenes participate only at much higher temperatures (e.g. 140–150 °C) and usually produce very low yields of cyclopentenones."


**Alkene Reactivity**

*Alkene Strain Impact*

\[ \text{[Diagram]} \]

- a. \( R^1 = R^2 = H \)
- b. \( R^1 = H, R^2 = \text{Me} \)
- c. \( R^1 = H, R^2 = \text{Ph} \)
- d. \( R^1 = \text{Me}, R^2 = \text{Ph} \)
- e. \( R^1 = R^2 = \text{Et} \)
- f. \( R^1 = R^2 = \text{Ph} \)

---


**Alkene Reactivity**

*Ethylene and Equivalents*

\[ \text{[Diagram]} \]

- Cycloalkenes possible at higher temp (60 – 120 °C)
- 5 and 7 rings work best
- 6 ring is "sluggish"

**Alkene Reactivity**

*Examples En Route to Prostaglandins*

![Chemical structure](image)

**Table: Alkene Reactivity**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₄CO₂Me</td>
<td><img src="image" alt="Product 1" /></td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>CH₂CH=C₃H₄CO₂Me</td>
<td><img src="image" alt="Product 2" /></td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₄CO₂Me</td>
<td><img src="image" alt="Product 3" /></td>
<td>33</td>
</tr>
</tbody>
</table>


---

**Intramolecular PKR**

*First Publications*

**First Intramolecular PKR**

— Originally reported by Neil E. Schore in 1981  
— University of California, Davis  
— 1st Paper Focus: Synthesis of Vinyl Ether and Ester Enynes  
— 2nd Paper Focus: Intramolecular PKR

"Unfortunately, unstrained alkenes are considerably less reactive in this cyclization process, thus severely limiting its generality: simple olefins react only under forcing conditions, and the yields of cyclopentenones obtained vary greatly. We suspected, however, that the intramolecular disposition of the functional groups in a,w–enynes might enhance the desired mode of reactivity."

![Neil E. Schore](image)

**Articles**


**Intramolecular PKR**

*First Publications*

![Chemical structures and reactions](image)


---

**Intramolecular PKR**

*Thorpe–Ingold Precursors*

![Chemical structures and reactions](image)

"While yield of the cyclopentenones, whether formed inter– or intramolecularly, are relatively modest, we felt that this could be easily improved by choice of appropriate substituents connecting alkyne and alkene.

Undoubtedly, the Co₂(CO)₉ mediated conversion . . . should greatly benefit from the *gem*-methyl group (Thorpe–Ingold effect) . . ." [bold added]

**Intramolecular PKR**

*Influence of Substituents*

\[ \text{R} = \text{TMS} \text{ or H (80 °C, 48 h)} \]
\[ \text{R} = \text{MOM (125 °C, 36 h)} \]
\[ \text{R} = \text{(CH\textsubscript{3})\textsubscript{2}OMOM (115 °C, 36 h)} \]

\[ \text{R} = \text{TMS, Me, H (55:45)} \]
\[ \text{R} = \text{TMS, Me, H (25:75)} \]
\[ \text{R} = \text{TMS, Me, H (78:22)} \]

**Intramolecular PKR**

*Influence of α-Substituent*

\[ \Delta \]

\[ \text{R} = \text{TBS OR H (80 °C, 48 h)} \]
\[ \text{R} = \text{MOM (125 °C, 36 h)} \]
\[ \text{R} = \text{(CH\textsubscript{3})\textsubscript{2}OMOM (115 °C, 36 h)} \]

**Intramolecular PKR**

*Influence of α-Substituents*

![Chemical structure](image)

---

**PKR Intramolecular**

*Other Substrates*

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>90</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>86</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>69</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>87</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>(CH₂)₂OPTH</td>
<td>92</td>
<td>41</td>
</tr>
</tbody>
</table>

---


**PKR Intramolecular**

*Other Substrates*


---

**PKR Mechanism**

*DFT Calculations*

**PKR Mechanism**

*Lowering $E_a$*

---

**Increasing Reaction Rate**

- Substrate assisted dissociation
- Increase rate of CO removal
- Oxidize CO → CO$_2$
- Ligand Substitution
- Induce CO Dissociation
- Stabilize intermediates

**Additives**

- Increase rate of CO removal
  - Irradiation, microwave
  - Tertiary Amine N-Oxides (TMO, NMO)
  - Phosphine Oxides, Phosphines, Sulfoxides,
    Sulfides, Thioacetals, Nitriles, Amines, Thioureas
- Stabilize intermediates
  - SiO$_2$, Al$_2$O$_3$
  - Molecular Sieves

---

**Electronic Effects**

*Substrate Assisted Dissociation*

---


---

Additives
Photoinduced CO Dissociation

Additives
Photoinduced CO Dissociation
Additives
Tertiary Amine N–Oxides

Details
— Indications of Decarboxylation with N–Oxides

\[(\text{CO})_5\text{FeL} \rightarrow \text{L} + \text{NR}_3 + \text{CO}_2 + \text{"Iron Compounds"}

\]
Shi and Baslow, Organometallics 1987, 6, 1528–1531.
Shi and Baslow, Organometallics 1989, 8, 2144–2147.
— First suggested by Pauson in 1988 ("erratic results")

— Further development by Nakcheol Jeong

"... encountered some limitations because of its intrinsic
problems in reaction conditions such as requiring high
temperature (usually 60–120 °C) and long reaction time
(6h – 4 days).

... we envisioned that these reagents [tertiary amine N–
oxides] could serve as promoters to generate vacancy for
incoming olefins and accelerate the overall reaction."

Jeong, Synlett 1991, 204–206
— NR$_3$ removable by evaporation

Additives
Tertiary Amine N–Oxides

<table>
<thead>
<tr>
<th>entry</th>
<th>Conditions</th>
<th>% Yield</th>
<th>Product</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMANO (3 equiv), O$_2$, DCM, 3 h</td>
<td>90</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CAN (3 equiv), DCM, 16 h</td>
<td>32</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CAN (3 equiv), acetone, 3h</td>
<td>0</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NMO (3 equiv), DCM, 8 h</td>
<td>87</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Tertiary Amine N–Oxides

**Intermolecular**

![Diagram](image1)

<table>
<thead>
<tr>
<th>entry</th>
<th>Alkyne</th>
<th>Alkene</th>
<th>Product</th>
<th>% Yield</th>
<th>Catalyzed</th>
<th>Uncatalyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td></td>
<td><img src="image2" alt="Phoxide" /></td>
<td>80 (83:17 = exo:endo)</td>
<td>45 (exo only)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td><img src="image3" alt="alkene" /></td>
<td><img src="image4" alt="alkeneoxide" /></td>
<td>80</td>
<td>74 Inseparable</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(CH₂)OH</td>
<td><img src="image3" alt="alkene" /></td>
<td><img src="image4" alt="alkeneoxide" /></td>
<td>93 (88:12 = exo:endo)</td>
<td>69 (exo only)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>OR</td>
<td><img src="image4" alt="alkeneoxide" /></td>
<td>R = H</td>
<td>64 (2:1)</td>
<td>Not Provided</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>OR</td>
<td><img src="image4" alt="alkeneoxide" /></td>
<td>R = THP</td>
<td>30 (3:1)</td>
<td></td>
</tr>
</tbody>
</table>


### Tertiary Amine N–Oxides

**Intramolecular**

![Diagram](image5)

<table>
<thead>
<tr>
<th>entry</th>
<th>Alkyne</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image6" alt="alkyne" /></td>
<td><img src="image7" alt="product" /></td>
<td>85 (14°)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image6" alt="alkyne" /></td>
<td><img src="image7" alt="product" /></td>
<td>92 (29°)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image6" alt="alkyne" /></td>
<td><img src="image7" alt="product" /></td>
<td>70 (5:1)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image6" alt="alkyne" /></td>
<td><img src="image7" alt="product" /></td>
<td>86 (5:1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image6" alt="alkyne" /></td>
<td><img src="image7" alt="product" /></td>
<td>68 (11:1)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="alkyne" /></td>
<td><img src="image7" alt="product" /></td>
<td>83</td>
</tr>
</tbody>
</table>

*Uncatalyzed yields.*

Additives

Tertiary Amine N-Oxides

Review Articles

Articles
Kerr, Organometallics 1995, 14, 4986–4988.

Additives

Phosphorous Compounds

\[
\text{PhMe, Reflux Conditions}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>L¹</th>
<th>L²</th>
<th>Time (h)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO</td>
<td>CO</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>2ᵃ</td>
<td>PPh₃</td>
<td>CO</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>P(Ph)₃</td>
<td>CO</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>P(OMe)₃</td>
<td>CO</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>P(OMe)₃</td>
<td>CO</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>PhP⁻Ph₂</td>
<td>CO</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>7ᶜ</td>
<td>Bu₃PO</td>
<td>CO</td>
<td>36</td>
<td>69 (36⁹)</td>
</tr>
</tbody>
</table>

ᵃ Reflux in PhH. ᵇ Based on > 10% recovery. ᶜ Reflux in hexane. ᵈ Uncatalyzed yield.

### Additives

#### Amines

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-hexane</td>
<td>35</td>
<td>3 d</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>35</td>
<td>3 d</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1,2-dichloroethane</td>
<td>35</td>
<td>3 d</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1,4-dioxane</td>
<td>35</td>
<td>3 d</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>35</td>
<td>3 d</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Et$_2$N</td>
<td>35</td>
<td>3 d</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Et$_2$NH</td>
<td>35</td>
<td>3 d</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>n-PrNH$_2$</td>
<td>35</td>
<td>5 min</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>i-PrNH$_2$</td>
<td>35</td>
<td>5 min</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>CyNH$_2$</td>
<td>35</td>
<td>5 min</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>t-BuNH$_2$</td>
<td>35</td>
<td>3 d</td>
<td>54</td>
</tr>
</tbody>
</table>

**Amine Impact**

- Amines act as hard ligands to:
  - Displace CO
  - Activate Alkynes
- Primary amines work best
- Also investigated NH$_4$OH
  - 1,4-dioxane/NH$_4$OH sol (1:3 v/v) works best
  - High yields and fast run time

---

### Additives

**Silica Gel (DSAC)**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Silica Gel Example</strong></td>
<td>Tetrahedron Lett. 1986, 27, 1241–1244</td>
<td></td>
</tr>
<tr>
<td>- <strong>First reported by W. A. Smit in 1986</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Dry State Adsorption Conditions (DSAC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>SiO₂ (mostly used) and Al₂O₃ (pH independent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>10–20% H₂O Optimal; 5–30% H₂O Inactive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Substrate must have polar groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Procedure</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Add silica gel</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Evaporate solvent</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Heat under appropriate gas</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Reaction finished when silica turns gray</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Increase reaction rate</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Interaction of polar groups with silica surface limits molecular movement (ΔΔS), bringing the alkene and alkyne closer together</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Surface displace carbonyl ligands</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Increasing Rate</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Marco–Contelles, Organic Preparations and Procedures Int. 1998, 30, 121–143.

### Additives

**SiO₂ and Al₂O₃ (DSAC)**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Substrate must have polar groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Procedure</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Add silica gel</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Evaporate solvent</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Heat under appropriate gas</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Reaction finished when silica turns gray</strong></td>
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<td></td>
<td><strong>Increase reaction rate</strong></td>
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<tr>
<td></td>
<td>- <strong>Interaction of polar groups with silica surface limits molecular movement (ΔΔS), bringing the alkene and alkyne closer together</strong></td>
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</tr>
<tr>
<td></td>
<td>- <strong>Surface displace carbonyl ligands</strong></td>
<td></td>
</tr>
</tbody>
</table>

## Additives

### Silica Gel (DSAC)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Temp (°C)</th>
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## Additives

### DSAC References

**Review Articles**


**Articles**

PKR Review References

Review Articles


